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A COMPUTER SIMULATION OF CONDUCTION IN DEMYELINATED NERVE FIBRES

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SUMMARY

1. The theoretical effects of demyelination on conduction of a propagated impulse have been examined in a computer simulated myelinated nerve fibre. Demyelination was simulated by increasing the capacitance and conductance of the myelin sheath of individual internodes or parts of internodes.

2. Internodal conduction time increased as myelin thickness was decreased. The increase in internodal conduction time became more precipitous as the myelin became thinner. Propagation continued past a single demyelinated internode until myelin thickness was uniformly reduced to less than 2·7 % of normal myelin thickness.

3. Paranodal demyelination was more effective in slowing impulse conduction than was uniform demyelination of an entire internode with an equivalent rise in overall internodal capacitance and conductance.

4. The effects on conduction of demyelination of two adjacent internodes or of two internodes separated by a normal internode were more than the sum of the effects of demyelination of each internode individually.

5. Propagation across a severely demyelinated internode was blocked with an increase in internal sodium concentration which had a trivial effect on conduction in a normal fibre.

6. Propagation across a severely demyelinated internode was blocked

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with increased temperature at a temperature at which propagation proceeds normally across normal internodes.

7. The similarity between the findings of the computer simulations and the experimental findings in demyelinated fibres is discussed.

INTRODUCTION

Experimental studies of conduction in demyelinated single nerve fibres have established that conduction remains saltatory in demyelinated fibres, the decreased conduction velocity being due to an increase in internodal conduction time of affected internodes (Rasminsky & Sears, 1972). Although it can be inferred from the form of the records of external longitudinal current obtained from the demyelinated fibres that the increase in internodal conduction time is due to an increase in myelin capacitance and conductance, technical considerations precluded accurate determination of these quantities (Rasminsky & Sears, 1972). In order to examine the effects of changes in myelin capacitance and resistance on conduction, these values were manipulated in a computer simulated myelinated nerve fibre.

Previous computer simulations of propagating action potentials in amphibian myelinated fibres have shown excellent agreement with experimental findings (Goldman & Albus, 1968; Hutchinson, Koles & Smith, 1970). In the first attempt to simulate conduction in a demyelinated fibre, Smith & Koles (1970) examined the effect of uniform reduction of myelin thickness over the entire length of the fibre. They found that conduction continued until the ratio of axonal diameter/fibre diameter was increased to 0·95, that is until myelin thickness was between 5 and 6% of normal. The lowest conduction velocity obtained was 22% of that of a fibre of normal dimensions.

Smith & Koles (1970) recognized that uniform reduction of myelin thickness offered only a very rough first approximation of the situation in real demyelinated fibres in which successive internodes are not uniformly affected and in which the pathological changes may be found primarily in the paranodal regions rather than uniformly distributed throughout the internodes. In the light of the finding that slowing of conduction is indeed not uniform at successive internodes of single demyelinated fibres (Rasminsky & Sears, 1972) it was thought that it would be of interest to examine the effects of demyelination of individual internodes on conduction of a propagated impulse in a simulated fibre.

As insufficient data for mammalian nodes and internodes is available it was necessary to use data from frog and toad fibres (Tasaki, 1955; Frankenhaeuser & Huxley, 1964). The limited data available on mam-

malian nodes (Maruhashi & Wright, 1967; Horáckova, Nonner & Stämpfli, 1968) suggest that within broad limits, mammalian nodes resemble amphibian nodes in all respects except in the time scale of active nodal processes.

METHODS

The model system

The model was similar to that originally described by Fitzhugh (1962) and subsequently modified by Goldman & Albus (1968). The model fibre consisted of twenty-one nodes (numbered node 0 to nodes ± 10) and twenty internodes. At nodes ± 10 the exterior of the fibre was short circuited to the interior. The myelin sheath of each internode was represented by nine elements of parallel capacitance and conductance. Each element could be independently manipulated. Myelin capacitance and conductance were both assumed proportional to $1/\log_e (D/d)$ where D and d were fibre diameter and axon diameter respectively. These relationships are those for the

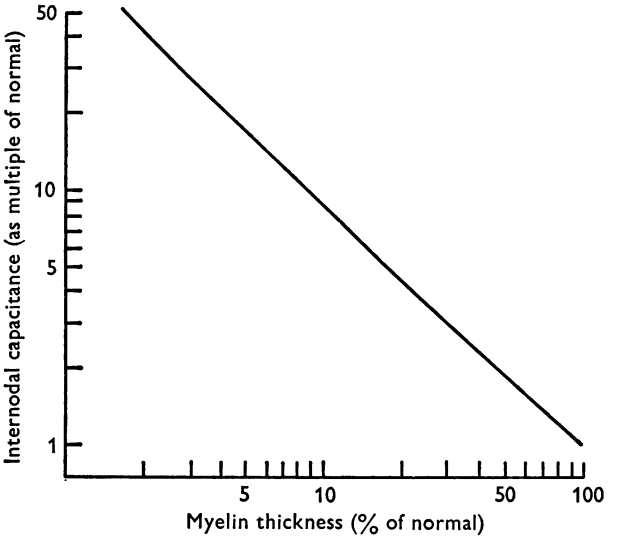

Fig. 1. Theoretical relationship between myelin capacitance (or conductance) and myelin thickness for the model fibre. Note logarithmic co-ordinates.

capacitance and conductance of a cylinder; this theoretical relationship between myelin thickness and myelin capacitance (and/or conductance) is illustrated in Fig. 1. A small change in myelin thickness will have relatively little effect on myelin capacitance when the total thickness is near normal but will have a marked effect when the thickness is already small.

The internal axoplasm was represented by ten identically resistive elements. External longitudinal resistance was assumed to be negligible.

The equation system to be solved for a propagated action potential in a myelinated nerve fibre has been given by Goldman & Albus (1968) who used data given by Tasaki (1955) and Frankenhaeuser & Huxley (1964). The data list used for the

computations presented in this paper was the same. The normal model fibre was considered to have an axon diameter of 10·5 μm, a fibre diameter of 15 μm, an internodal length of 1·38 mm and a nodal gap width of 2·5 μm. Temperature was 20° C unless specified otherwise.

Computations were carried out on the CDC 6600 computer of the University of London using a 4th order Runge–Kutta numerical integration technique. The step size used was modified dynamically by the devised algorithm to maintain the difference (the error) between the solution obtained by advancing one time increment and that obtained by advancing two half time increments at less than 0·01 mV in the membrane potential and at less than 10^{-4} in the activation and inactivation variables. Impulses were initiated by a 0·15 msec rectangular current stimulus applied at node 0. The potential changes between the axis cylinder and the external medium were observed at the nodes of Ranvier and at each of the nine evenly spaced internodal positions. Internodal conduction time was determined as the time between the 55 mV levels of the leading edges of the action potential at successive internodes.

Simulation of demyelinated fibres

It was assumed that demyelination effected no change in the area of the electrically excitable nodal membrane, its physiological properties and in the axon diameter. The effect of focal demyelination was examined by (1) uniformly reducing myelin thickness within one or more internodes, and (2) reducing myelin thickness within one or two internodal elements adjacent to node 5 on either or both sides of the node. This should more closely approximate the situation found in paranodal demyelination.

The effects of changes in temperature and changes in internal sodium concentration on conduction in fibres with demyelinated internodes were also examined. The temperature coefficients of the rate constants and permeability constants in the Frankenhaeuser–Huxley equations were taken from Frankenhaeuser & Moore (1963) and Frankenhaeuser (1965). Temperature coefficients of the capacitance of myelin and nodal membrane and the conductance of myelin, nodal membrane and axoplasm were assumed to be negligible.

RESULTS

In the normal fibre conduction proceeded at a uniform velocity between nodes 2 and 8. Normal internodal conduction time was 0·074 msec (Fig. 2).

Demyelination of a single internode

Fig. 3*a* illustrates the action potential at nodes 0 and 2 to 8 when internode 4–5 (the internode between nodes 4 and 5) was uniformly demyelinated to 2·7 % of its normal myelin thickness. The internodal conduction time of internode 4–5 was 0·92 msec which is 0·85 msec more than (or 12·5 times as much as) the normal internodal conduction time. The total delay due to demyelination of a single internode is in fact greater than this as can be shown by comparing the conduction time between nodes 2 and 8 for the demyelinated and normal fibres. Conduction time from node 2 to node 8 was 0·44 msec for the normal fibre and 1·44 msec when internode 4–5 was demyelinated to 2·7 % of its normal thickness. The difference between these is 1·00 msec; this is somewhat more than the 0·85 msec increase in the internodal conduction time of internode 4–5.

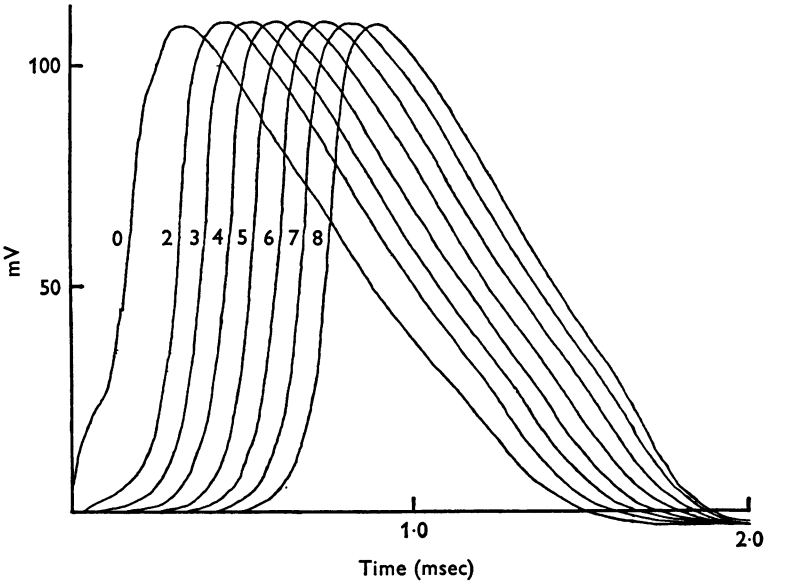

Fig. 2. Propagated action potential in simulated normal fibre at nodes 0 and 2 to 8. The impulse is initiated by a 0·15 msec stimulus at node 0.

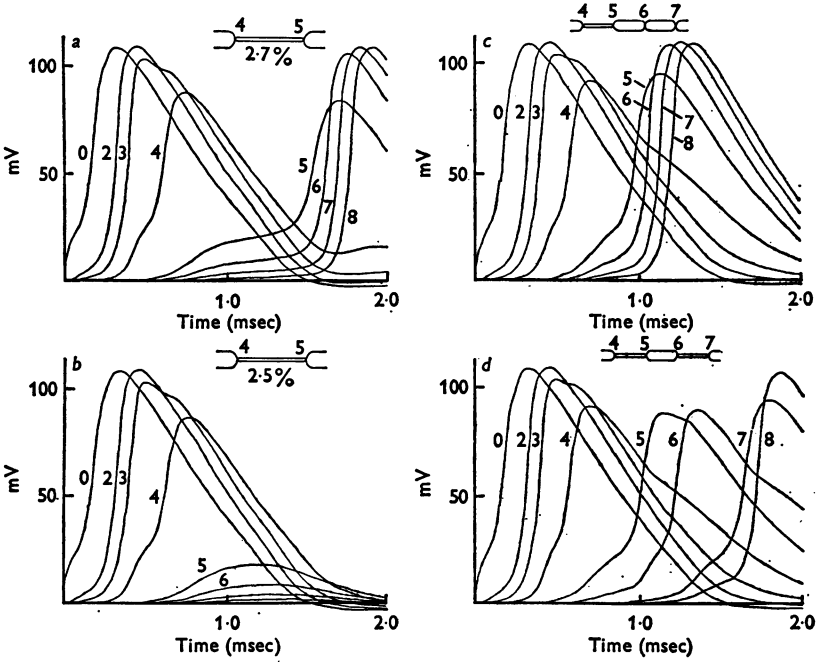

Fig. 3. Propagated action potential in simulated fibre at nodes 0 and 2 to 8. *a*, internode 4–5 demyelinated to 2·7% of normal myelin thickness. *b*, internode 4–5 demyelinated to 2·5% of normal myelin thickness. *c*, internode 4–5 demyelinated to 4% of normal myelin thickness. *d*, internodes 4–5 and 6–7 demyelinated to 4% of normal myelin thickness.

Fig. 3*b* shows failure of the impulse to propagate past node 4 when the myelin thickness of internode 4–5 was reduced to 2·5% of normal. Fig. 4 illustrates the relationship between internodal conduction time and myelin capacitance (and conductance) for the single internode 4–5, all other internodes in the fibre being normal.

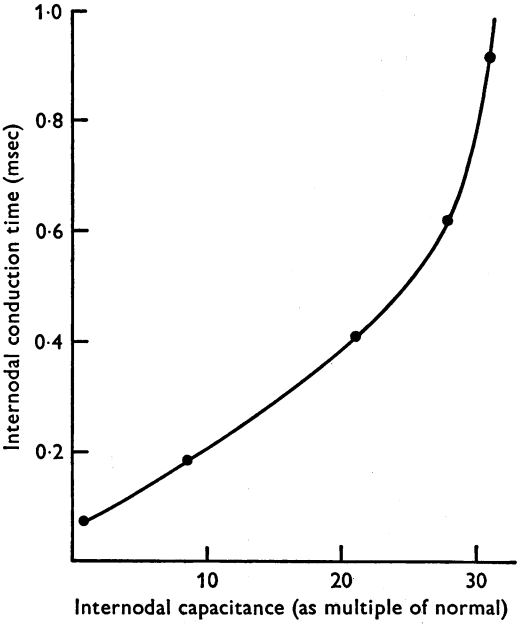

Fig. 4. Variation of internodal conduction time with myelin capacitance (and conductance) for internode 4–5 of simulated fibre. Variation of internodal conduction time with myelin thickness can be estimated by comparison of this graph with Fig. 1.

Paranodal demyelination

In the initial stages of demyelination, myelin break-down is confined to the paranodal region (Ballin & Thomas, 1968; Allt & Cavanagh, 1969). It was thus thought that it would be of interest to examine the effect of paranodal demyelination on conduction in the simulated fibre. Each internodal element of parallel myelin capacitance and conductance represents one ninth of the total internodal myelin. The effect of paranodal demyelination was initially simulated by changing myelin thickness in the two most distal elements of internode 4–5. It was found that propagation continued until myelin thickness of the distal two ninths of the single internode was reduced to 0·8% of normal but failed when myelin thickness was reduced to 0·75% of normal. Internodal conduction time of internode 4–5 just before

failure was 0·73 msec. Conduction proceeded with a virtually identical delay when myelin thickness of the distal one ninth of internode 4–5 was reduced to 0·4 % of normal.

The polarity of paranodal demyelination in relation to the node is evidently of considerable importance. Fig. 5*a–c* illustrates the effect of reducing myelin thickness to 0·8 % in the two elements of internode 4–5 immediately proximal to node 5, in one element on either side of node 5 and in the two elements of internode 5–6 immediately distal to node 5. Although the amount of myelin removed was the same in each case, the over-all delay of conduction was greatest when the paranodal demyelination was on both sides of the node and least when it was exclusively distal to the node.

Paranodal demyelination was more effective in slowing impulse conduction than was uniform demyelination of the entire internode with an equivalent rise in over-all internodal capacitance and conductance. Reduction of myelin thickness in a single element of 0·8 % of normal results in an increase in the capacitance (and conductance) of that element of 104·5 times normal. If two elements are demyelinated the over-all capacitance (and conductance) of the entire internode is $\frac{1}{9}(2 \times 104{\cdot}5 + 7) = 24$ times normal, since the individual elements can be thought of as capacitances and conductances in parallel. A twenty-four-fold increase in internodal capacitance would give rise to an internodal conduction time of 0·48 msec. (Fig. 4) which is considerably less than the 0·73 msec found on proximal paranodal demyelination of two elements to 0·8 % of normal thickness.

In the cases of both demyelination of an entire internode and of paranodal demyelination, the action potentials generated at the nodes bordering the demyelinated internode(s) are reduced in amplitude and have a decreased maximum slope. As the active nodal properties in this model are those of normal nodes it is clear that abnormal nodal action potentials recorded from actual demyelinated fibres cannot be construed *per se* as evidence of nodal abnormality (see Rasminsky & Sears, 1972).

The form of the action potentials of demyelinated fibres

In Fig. 3*a* it is apparent that the action potentials at nodes 3 to 6 all have discontinuities which are not apparent at nodes of the normal fibre. The discontinuities are not so clearly apparent at nodes 7 and 8 but both these nodes have an inordinately prolonged initial slow change of potential. The potential generated at node 4 electrotonically decrements in both directions. This is reflected by the discontinuities on the falling phase of the action potential at node 3 and on the rising phase of the action potentials at nodes 5 and 6. The discontinuity on the rising phase of the action potential at node 5 is strikingly later than the maximum potential excursion

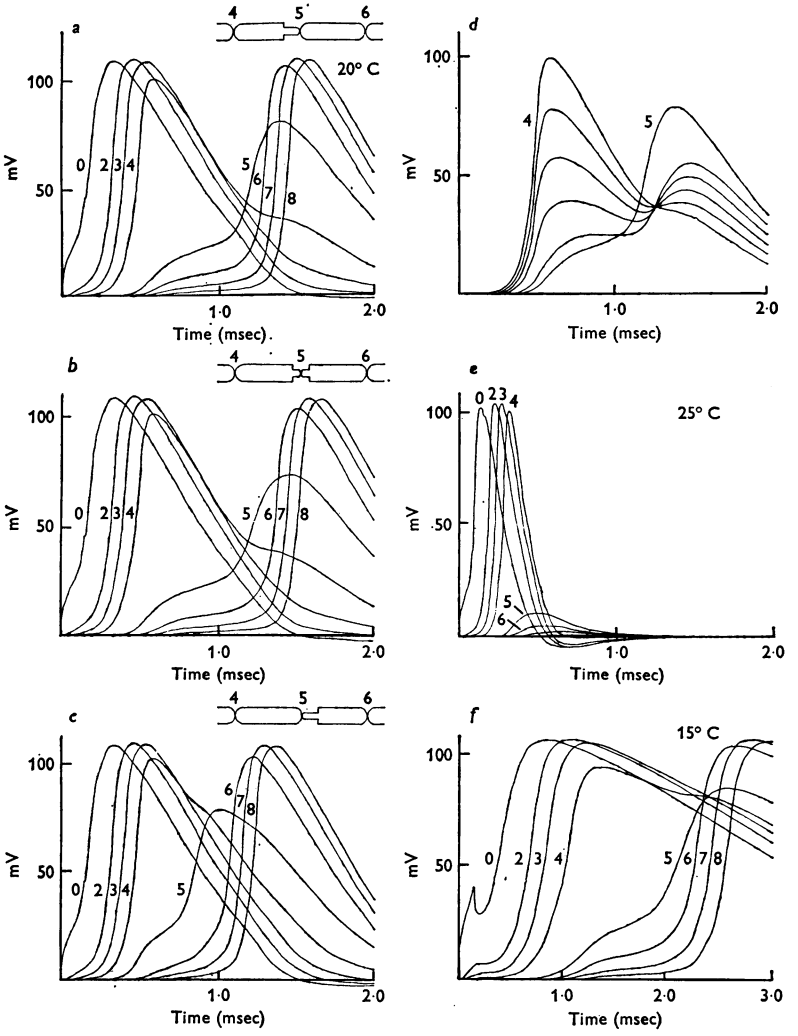

Fig. 5. Propagated action potential in simulated fibres. The effects of paranodal demyelination and changes in temperature. *a–c*, paranodal demyelination of two internodal elements to 0·8 % of normal thickness: *a*, proximal to node 5, *b*, straddling node 5, *c*, distal to node 5, *d*, paranodal demyelination as in *a*, propagated action potential at nodes 4 and 5 and four evenly spaced internodal points. *a–d*, all at 20° C. *e*, paranodal demyelination as in *a* at 25° C. *f*, paranodal demyelination as in *a* at 15° C (note difference in time scale).

at node 4. This is due to the delay caused by the greatly increased capacitance of internode 4–5. The striking electrotonic decrement in amplitude is due to the greatly increased myelin conductance of the internode 4–5. The very slow initial change in the potentials at nodes 7 and 8 is due to the potential electrotonically decremented from node 4. This electrotonically decremented potential is insufficient to bring nodes 7 and 8 to threshold; consequently the potential rise at nodes 7 and 8 is very slow until the effects of the potentials generated at nodes 5 and 6 begin to become manifest.

Discontinuities due to the spatial and temporal separation of potential or current generating sites are even more striking for the internodal records illustrated in Fig. 5*d*. The potential at each internodal point has two major humps related to activity at the proximal and distal nodes respectively. The form of the internodal action potentials from the simulated demyelinated fibres is strikingly similar to those found experimentally (Rasminsky & Sears, 1972).

All of the discontinuities which have just been discussed are exaggerated versions of the discontinuities apparent in the action potentials of normal myelinated fibres (Stämpfli & Zotterman, 1951; Hodler, Stämpfli & Tasaki, 1952; Fitzhugh, 1962) which are a consequence of the spatial and temporal separation of sites of excitable membrane.

Demyelination of more than one internode

The cumulative effect of demyelinating more than one internode is illustrated in Fig. 3*c*, *d*. When internode 4–5 was demyelinated to 4% of normal myelin thickness the conduction time between node 2 and node 8 was 0·88 msec, i.e. 0·44 msec greater than normal. When both internode 4–5 and internode 6–7 were demyelinated to 4% of normal myelin thickness the conduction time between node 2 and node 8 was 1·40 msec, i.e. 0·96 msec greater than normal. This is 0·08 msec (i.e. 9%) more than the delay to be expected from demyelination of two internodes if the effects of each internode on conduction were completely independent of the effect of other internodes. However, the interaction between two demyelinated internodes was shown most vividly by the failure of the impulse to propagate to node 5 when both internode 4–5 and internode 5–6 were demyelinated to 4% of normal myelin thickness (not illustrated).

The effect of internal sodium concentration

Under standard conditions in the model, internal sodium concentration was 13·7 mM. The effect of changing internal sodium concentration was observed in the model fibre illustrated in Fig. 3*a* (internode 4–5 demyelinated to 2·7% of normal myelin thickness). When internal sodium concentration was raised to 14·7 mM the conduction time between node 2 and

node 8 increased from 1·44 to 1·54 msec. Propagation to node 5 failed when the internal sodium concentration was raised to 15·7 mM. At normal internodes internodal conduction time with an internal sodium concentration of 15·7 mM was 0·075 msec, only 1% greater than that under standard conditions.

The effect of temperature

Conduction velocity increases with increasing temperature in normal myelinated fibres (Frankenhaeuser & Waltman, 1959; Paintal, 1965). Hutchinson *et al.* (1970) have shown that the experimentally demonstrable linear relationship between conduction velocity and temperature is predicted by computer simulation of a frog myelinated fibre. Experimental studies on demyelinated single fibres suggest that internodal conduction time may be decreased with increased temperature at less severely demyelinated internodes and that conduction may be blocked with increased temperature at severely demyelinated internodes (Rasminsky, 1971).

The effect of change in temperature on a simulated fibre with a severely demyelinated internode is shown in Fig. 5*a*, *e*, *f*. In a fibre with the distal two elements of internode 4–5 demyelinated to 0·8% of normal myelin thickness, propagation across internode 4–5 was just on the point of failure at 20° C. At 25° C propagation failed at node 5; at 15° C propagation past node 5 occurred and the internodal conduction time for internode 4–5 was significantly greater than at 20° C.

DISCUSSION

The question arises as to how accurately the model reflects the situation in an actual demyelinated fibre. In order to assess the importance of possible disparities between the model and real fibres the more important assumptions explicit and implicit in the model will be reviewed:

(1) *Excitability remains confined to the nodes in demyelinated fibres and dimensions of the electrically excitable nodal membrane are those of normal fibres.* Experimental studies indicate that a form of saltatory conduction persists in demyelinated fibres; the possibility remains open that there is continuous conduction over short lengths of paranodal axon (Rasminsky & Sears, 1972).

(2) *Properties of nodal membrane remain unchanged in demyelinated fibres.* There can be no question that excitable membrane of demyelinated fibres generates currents comparable in magnitude to those generated by nodes of normal fibres (Rasminsky & Sears, 1972). No experimental comparison has been made of the ion permeability changes at nodes of normal and demyelinated fibres.

(3) *The myelin sheath can be adequately represented as a cylinder with dielectric constant and specific resistance unaffected by changes in thickness.* Pathological studies have made it clear that myelin is not stripped off a whole internode lamella by lamella during demyelination. The thickness of myelin may vary considerably from one portion of an internode to the next. The spacing between intact lamellae may vary and structures such as monocytes and macrophages may be interposed between lamellae (see e.g. McDonald, 1967). For convenience myelin capacitance and conductance have been assumed not to vary independently. This may not always be strictly the case. The cylinder of manipulable thickness is a convenient approximation which presumably most closely approaches the real situation for the extremes of intact myelin and virtually complete segmental demyelination.

(4) *The axon constitutes a cylinder of constant radius.* There is ample anatomical evidence to indicate that this is not in fact the case. Local decrease in axon thickness in demyelinated fibres (Denny-Brown & Brenner, 1944*a*, *b*; McDonald, 1963) would cause an increase in axoplasmic longitudinal resistance since the longitudinal resistance is inversely proportional to the cross-sectional area. Such local increases in axoplasmic resistance could be introduced into the model with predictable results. Longitudinal current would be diverted through the myelin with consequent increase in internodal conduction time or, in the extreme case, conduction block.

(5) *Specialization of nodal and paranodal structures are of no relevance to the conduction process.* It has been suggested that the close apposition of axolemma and myelin in the paranodal area is of importance in directing current flow towards the nodes (Robertson, 1959, 1960 and others). No similar device is incorporated into the model. Other nodal specializations may be of some importance in maintaining a constant nodal microenvironment (Landon & Williams, 1963; Williams & Landon, 1963; Berthold & Skoglund, 1967; Berthold, 1968; Langley & Landon, 1968); internal and external electrolyte concentrations have been held constant in the model.

(6) *Mammalian fibres resemble amphibian fibres in all respects except in the time scale of active nodal processes.* The limited data available on mammalian nodes (Maruhashi & Wright, 1967; Horáckova, Nonner & Stämpfli, 1968) suggest that this is not unreasonable.

In so far as mammalian single fibres can be regarded as passive cable of variable capacitance and conductance interspersed with sites of active membranes, the model should provide at least a qualitative indication of the nature of conduction abnormalities to be expected in demyelinated nerve. Experimentally demyelinated internodes were found to sustain internodal conduction times of up to 25 times normal (Rasminsky & Sears,

1972) whereas the model fibre was able to sustain an internodal conduction time of 12·5 times normal. This discrepancy could be related to differences in the nature of the ion permeability changes at amphibian and mammalian nodal membranes and/or to differences in the cable properties and ratio of nodal to internodal capacitance in amphibian and mammalian fibres. It is clear from Figs. 1 and 4 that when myelin thickness is small, relatively small changes in thickness will cause large changes in already greatly increased myelin capacitance and conductance; this will in turn cause relatively large changes in internodal conduction time. Thus the difference between the maximum increase of internodal conduction time tolerated by the model on the one hand and by real mammalian fibres on the other does not necessarily imply a very substantial difference between the real and model fibres, except for the acknowledged one of time scale.

The importance of the interaction between events at successive internodes is made clear by a comparison of the present findings to those of Smith & Koles (1970) who examined the effect of uniform demyelination of all internodes of a similar model. In that situation conduction failed when myelin thickness was only 5–6% of normal and minimal velocity was more than a fifth of normal, i.e. maximal internodal conduction time was less than five times normal. Propagation can continue past much more severely demyelinated single internodes if the adjacent internodes are relatively normal.

The striking sensitivity of demyelinated internodes to minimal changes in internal sodium concentration is illustrated by the model. There is strong inferential evidence that such changes in internal sodium concentration actually occur and cause conduction block in demyelinated fibres transmitting trains of impulses (Rasminsky & Sears, 1972).

The effect of changes in temperature on conduction in simulated demyelinated fibres is in gratifying agreement with the experimental findings (Rasminsky, 1971) both in demonstrating conduction block at affected internodes with increased temperature and increased internodal conduction time at affected internodes (as at normal internodes) with decreased temperature.

Some of the quantitative conclusions of the simulations bear further brief comment. The model does not distinguish between myelin lamellae and internodal axolemma; in fact it is likely that the dimensions and passive electrical properties of unit axon membrane and unit Schwann cell membrane are very similar. In the model fibre 2·7, 0·8 and 0·4% of the normal myelin thickness of 2·25 μm are 600, 180 and 90 Å respectively. If unit membrane has a thickness of 85 Å (Robertson, 1960) these thicknesses correspond to axon membrane and six Schwann cell membranes, axon membrane and one Schwann cell membrane, and bare axon respec-

tively. In other words the model suggests that conduction can proceed across an internode if the entire internode is divested of all but three bilayers of compact myelin, if the distal two ninths of the internode is divested of all but one Schwann cell membrane, or if the axon is completely bare over one ninth of the internode.

These quantitative findings may be of some relevance in relation to human demyelinating diseases. The poor correlation between clinical and pathological findings in patients with multiple sclerosis is well known (see Mackay & Hirano, 1967; Namerow & Thompson, 1969). The computations suggest that extremely thinly myelinated axons may be capable of conducting impulses; the histological methods used in light microscopic neuropathology are inadequate to distinguish between thinly myelinated axons which would, and bare axons which would not conduct impulses. It thus seems entirely conceivable that in some cases impulses can in fact be conducted through most fibres in a plaque of demyelination; this would explain the hitherto puzzling failure of some plaques in patients with multiple sclerosis to give rise to symptoms.

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